Mechanisms of disease: paracrine effects of adipose tissue, progenitor cell function, and epigenetics of diabetic vascular disease

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Adipose tissue has been recognized as a source of cytokines that contributes to chronic inflammation in patients with metabolic syndrome and diabetes.1,2 Furthermore, perivascular epicardial adipose tissue has been related to cardiovascular risk factors and coronary artery calcification,3 as well as to the severity of coronary artery disease.4 Endothelial dysfunction is an early stage of atherosclerosis,5 and hence it is of interest to see how perivascular adipose tissue interferes with the control of vascular tone.

The first paper in this issue, entitled ‘Tumour necrosis factor-alpha participates on the endothelin-1/nitric oxide imbalance in small arteries from obese patients: role of perivascular adipose tissue’6 by Agostino Virdis from the University of Pisa in Italy assessed the impact of the cytokine tumour necrosis factor-alpha (TNF-α) produced by vascular and perivascular tissue on the endothelin-1 (ET-1)7 and nitric oxide (NO) system,8 which are both altered in many disease states. To that end, small arteries from 16 obese subjects and 14 controls were mounted in a pressurized myograph, and endogenous ET-1 activity was assessed by adding the ETA blocker BQ-123. The contributions of TNF-α and NO were tested using the anti-TNF-α antibody infliximab and the inhibitor of the L-arginine pathway L-NAME (N’-nitro-L-arginine methylester). Obese subjects showed a blunted L-NAME-induced vasoconstriction (reflecting a reduced basal NO release), which was augmented by infliximab, while the relaxation to BQ-123 (reflecting basal ET-1 production) was attenuated by infliximab but unaffected by L-NAME. Interestingly, removal of perivascular adipose tissue reversed these effects. Obese subjects also produced more superoxide, which was decreased by the NADPH oxidase inhibitor apocynin, L-NAME, and BQ-123, and abolished by infliximab. An increased vascular expression of ET-1, ETA, and ETA receptors, and higher vascular and perivascular TNF-α and TNF-α receptor expression was also noted.

Thus, in human obesity, early changes of the ET and NO system occur in response to an inflammatory cytokine produced in the vessel wall and perivascular adipose tissue, which may contribute to vascular disease and its complications such as myocardial infarction or stroke.

The second paper ‘Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines’9 by Stephane Hatem from Paris complements the findings of Virdis and co-workers. Not only perivascular, but also epicardial adipose tissue may affect coronary,10 and myocardial function,10 and, in turn, outcome. The aim of this study was to examine the effects of the secretome of human epicardial adipose tissue on the myocardium obtained from 39 patients. In organ culture, the epicardial adipose tissue secretome induced global fibrosis of rat atria. Activin A, a member of the transforming growth factor-beta (TGFβ) family involved in mesoderm induction, neural cell differentiation, bone remodelling, haematopoiesis, and reproductive physiology, was highly expressed in epicardial adipose tissue, particularly in those with reduced left ventricular function, and promoted atrial fibrosis, an effect blocked using neutralizing antibody. In sections of human atrial and ventricular myocardium, adipose and myocardial tissues were in close contact at sites of fibrosis. Thus, this is the first evidence that the secretome from human epicardial adipose tissue promotes myocardial fibrosis through the secretion of adipo-fibrokines such as activin A. Whether or not this will provide a novel therapeutic target in the future will have to be looked at in further studies.

Pluripotent stem cells have attracted a lot of attention recently as possible novel tools in regenerative medicine,11,12 albeit that this has resulted in mixed clinical results. This has led to the concept of restoring stem cell dysfunction ex vivo or in vivo by pharmacological means. In the third manuscript, ‘Pravastatin reverses obesity-induced dysfunction of induced pluripotent stem cell-derived endothelial cells via a nitric oxide-dependent mechanism’13 by Joseph C. Wu and colleagues from Stanford University investigated the dysfunction of progenitor cells in obesity. In their study, accompanied by a comprehensive Editorial by Francesco Paneni from the Karolinska Institute in Stockholm, Sweden,14 the authors compared the function of induced pluripotent stem cell-derived endothelial cells of normal mice, as well as of mice with diet-induced obesity (which were generated from tail tip fibroblasts).

In vitro functional analysis revealed that induced pluripotent stem cell-derived endothelial cells from obese mice exposed to a high fat diet had impaired capacity to form capillary-like networks, diminished migration, and lower proliferation and activated pathways involved in apoptosis, inflammation, and oxidative stress. Following hind limb ischaemia, mice receiving induced pluripotent stem cell-derived
endothelial cells obtained from mice with diet-induced obesity had decreased reperfusion compared with those injected with induced pluripotent stem cell-derived endothelial cells from normal mice. In the former, muscle atrophy and inflammatory cells were also noticed. When pravastatin was co-administered to mice receiving induced pluripotent stem cell-derived endothelial cells obtained from mice with diet-induced obesity, reperfusion increased, an effect that was blunted by co-administration of the NO synthase inhibitor, L-NAME. As a result, the authors for the first time provide evidence that induced pluripotent stem cell-derived endothelial cells from mice with diet-induced obesity exhibit endothelial dysfunction and reduced reperfusion in a hind limb ischaemia model. If confirmed at the clinical levels, this may have important implications for the future treatment of peripheral vascular disease in the obese population.

Diabetes often is a consequence of obesity and a major driver of cardiovascular disease. However, the underlying mechanisms remain at least in part elusive. In particular—and contrary to other risk factors such as hypertension and LDL-cholesterol—it remains unclear why a reduction of plasma glucose does not translate into a reduction of cardiovascular events. This has led to the concept of metabolic memory.

In the third paper, "Targeting prolyl-isomerase Pin1 prevents mitochondrial oxidative stress and vascular dysfunction: insights in patients with diabetes," Francesco Cosentino and colleagues from the Karolinska in Sweden and the University of Zurich try to address this issue by investigating the role of the prolyl-isomerase Pin1 in diabetes-induced vascular disease. Of note, Pin1 recognizes specific peptide bonds and modulates the function of proteins that regulate cellular homeostasis. In human aortic endothelial cells exposed to high glucose, up-regulation of Pin1 induced mitochondrial translocation of the pro-oxidant adaptor p66Shc and subsequent organelle disruption. In this setting, Pin1 also mediates hyperglycaemia-induced nuclear translocation of NF-κB p65, triggering the expression of the adhesion molecules vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and monocyte chemotactic protein-1 (MCP-1), and in turn vascular inflammation. Indeed, gene silencing of Pin1 in human endothelial cells suppressed p66Shc-dependent production of reactive oxygen species, restored NO availability, and blunted nuclear translocation of NF-κB. Consistent with these in vitro findings, diabetic Pin1−/− mice were protected against mitochondrial oxidative stress, endothelial dysfunction, and vascular inflammation. Importantl, increased expression and activity of Pin1 was also found in peripheral blood monocytes of diabetic patients and associated with impaired flow-mediated dilation, a clinical marker of endothelial dysfunction, as well as increased plasma levels of adhesion molecules. The authors therefore conclude that Pin1 drives diabetic vascular disease in mice as well as in humans and that this may provide novel strategies for interfering with the epigenetic mechanisms of metabolic memory.

Obesity and diabetes are often associated with increased levels of triglycerides, but their importance for risk assessment and management of such patients remains controversial. Indeed, triglyceride-rich lipoproteins have traditionally been considered a secondary risk factor for atherothrombosis, as HDL-cholesterol (HDL-C) correlates more consistently with cardiovascular risk. In a Current Opinion piece "Triglycerides on the rise: should we swap seats on the seesaw?" by Peter Libby from the Brigham and Women's Hospital in Boston, this issue is addressed. Adjustment of triglyceride concentrations for HDL-C attenuates their predictive value. This recently led to a focus on HDL-C whose concentrations vary inversely with those of triglycerides. Multiple strategies to raise HDL-C levels therapeutically have, however, failed to reduce events in clinical trials up until now, and genetic as well as clinical studies have also called into question the role of HDL particles as a causal risk factor. Of note, data from recent genetic studies have led to a re-examination of triglycerides as a cardiovascular risk factor rather than a marker. Two large, independent studies now provide strong evidence for a causal role for a constituent of a population of triglyceride-rich lipoproteins, apolipoprotein C3 (APOC3), in atherosclerotic vascular disease. This provides novel mechanistic insight, since APOC3 inhibits lipoprotein lipase, interferes with the clearance of triglycerides, and limits lipoprotein uptake by the liver. APOC3 may also have direct pro-inflammatory effects and promote endothelial apoptosis. These results have important clinical implications, and illustrate how genetic insights can guide our practice, challenge our preconceptions, point to new mechanisms, and ultimately usher in novel therapies to help our patients at risk.

The issue ends with a Current Opinion entitled "Simulation in cardiology: state of the art" by Jivendra Gosai from the University of Sheffield. Simulation training has existed for years in many professions, particularly aviation, but it now has also been taken up in cardiology. This is being driven by improvements in technology, shortened training time, and—above all—concerns about patient safety. The authors discuss the rationale behind simulation, the types of simulators available to the cardiologist, as well as faculty and quality requirements. The evidence for the use of simulation, including its role in improving technical skills and, as a consequence, clinical outcomes, as well as the pros and cons of this educational modality are discussed in detail.

The editors hope that this issue of the European Heart Journal will be of interest to its readers.

References


